



Mini Review : Issue of Heterotopic Ossification in Artificial cervical Disc Replacement

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Abstract : Heterotopic ossification is defined as the formation of extraskelatal bone in muscle and soft tissues.HO can also be defined as excessive bone tissue repair process . HO is a common complication of trauma ,burn and surgery .It should be more accurately defined as motion restricting and non motion restricting HO .There is no literature analysis available ,which could defined the potential surgical intervention and prosthesis - specific reason behind HO after Artificial – Cervical disc replacement surgery .Additionally , other possible predictors such as adjacent segment degeneration , Sagittarius alignment and operative levels may also play secretly in the process of Heterotopic Ossification .

In order to get a better understanding about HO occurrence ,mentioned information in this mini- review is useful for surgeons and patients both .On the other hand ,all selected studies in this review are lacking uniformity in nature .Hence the result of this review study should be considered prudently .

Key words : ACDR , TDR , HETEROTOPIC OSSIFICATION ,ARTIFICIAL CERVICAL DISC REPLACEMENT .

Introduction :Intervertebral Disc(IVD) act as main joints in vertebral column, providing both stability and flexibility to spine .Additionally , IVD facilitates bending , flexion ,torsion and assist to transmit loads applied to spine .Particularly , Nucleus Pulposus (NP) in IVD undergo extensive morphological and cellular changes in the course of Ageing.This process results in hardening of NP and a decrease in structural integrity , disc height , and flexibility of IVD .(1,2)

Anterior cervical discectomy and fusion (ACDF) has been described as a common method of surgical treatment for cervical radiculopathy since 1950s (3-5) and become the gold standard procedure .

Nonetheless , it was found that ACDF leads to increased mechanical load on adjacent segment by causing rigid fixation in motion segment .(6)

Ultimately , Artificial cervical disc replacement (ACDR) came to existence in order to preserve the mobility at index level.(7-11)

However , an adverse effect of Heterotopic ossification after ACDR has been reported for the first time in 2005 (12,13)

Apart from western medicine , Traditional Chinese Medicine (TCM) bandages , Indian Ayurvedic oil are very effective tool for the treatment of recurrent and traumatic lower back pain . In case of traumatic LBP (lower back pain) ,if the patient without any red flag sign,we should always opt conservative treatment with NSAID & muscle relaxant (Chlorzoxazone).(14) Two categories of treatment are available for disc degeneration disease (DDD). First modality is conservative treatment with no surgical methods , analgesics ,life style adjustment such as weight loss . If patient does not improve, he or she may opt second modality ie.surgical treatment . These surgical interventions are spinal fusion or disc arthroplasty .(15,16)

Commonly , results of several orthopaedic surgeries are uncertain , simple reason behind this fact is that surgeons can't avoid inevitable complications eg. Malunion , implant failure ,surgical wound infections , Heterotopic ossification , hematoma and spinal trauma in ACDR surgery. In recent scenario, no single method can be regarded as ideal for the treatment of all kind of pilon fractures . In addition ,surgeons' choice of method , experience etc. also play an important role in outcome of surgery.Therefore , we need to implement stem cell regenerative medicine (SCRM) in place of complicated surgeries with uncertain outcome. We can regenerate many damaged tissues , muscles , cartilage , bones ,brain tissues and enhance body's natural healing power through SCRM applications.Moreover, SCRM maybe a better emergency option to treat severe Covid- 19 patients .(17-23)

Material & Method : we search online database like google Scholar , web of Science ,pubmed ,springer , semantic scholar etc with key words like ,Heterotopic ossification , ACDR , TDR , ASD,Complication of ACDR. We reviewed 400 articles .Finally, we selected 234 article for writing this mini review .

Results : Results are shown in table1.

TABLE 1: INCIDENCE OF HETEROTOPIC OSSIFICATION IN ACDR

Author & year of publication	Total number of patients treated withACDR	Incidence of HO	Overall success of implant
Burna M etal (24)	39 patients	HO recorded in 10(25%) of cases with 5 of them classified as grade iii or iv.	Although number of patients diagnosed with HO growing, HO influences the clinical outcome only a little.
Yi S etal (25)	170 patients undergone ACDR Bryan disc -81 Patients Mobi C-61 Patients Prodisc C -28 Patients	Overall HO incidence was 40.6%(69 of 170 patients) Bryan disc group-21.0% Mobi C group 52.5% Prodisc Cgroup-71.4%	N/A
Guerin P etal (26)	71 patients undergone ACDR	HO was reported in 23 segments	N/A
Wu JC etal (27)	40 patients underwent ACDR	In 15 patients occurrence of HO was reported	Almost all artificial discs remained mobile(100%)& 95.8 % p=0.408
Tu TH etal(28)	36 patients underwent Bryan ACDR at 52 levels	On the basis of CT, HO was identified in 18(50%) of 36 patients & 25 (48.1%)of 52 levels treated. According to McAfee classification Grade ii- in 13 levels(25%) Grade iii- in 2levels(3.8%) Grade iv-in 1level(1.9) Nineteen (76%) of 25 affected levels were in	Patients who had HO had same clinical success rate as those who did not get HO occurrence(94.4%vs 94.4%, p=1.00) Visual analog scale (VAS) score for neck & arm pain were significantly improved in both HO & non HO group.

		patients who had undergone 2 level ACDR	
Wu JC(29)	Total 102 patients underwent bryan arthroplasty (single or multilevel) -86 patients completed followup	Multilevel group demonstrated higher rate of HO than the single level group(66% vs 25% p< 0.001)	The majority of (97.7%) of artificial discs in this series remained mobile despite of HO.
Mehren C etal(30)	54 Patients(total, 77 implanted prosthesis(ACD R-pro disc C)	In 26 treated segments (33.8%) no HO was detectable. Grade i HO- 6 levels(7.8%) Grade ii HO- 30 levels(39%) HO led to restricted range of motion in 8 cases (10.4%) Spontaneous fusion – 7 cases	49.4% patients were reported with HO (grade ii or grade iii) 33.8% patient-no HO Thus mobility of implanted segments need to be further investigated.
Chen j etal (31)	Literature were collected from pubmed, embase, conchrane library Original studies were eligible only if the HO is grade iii or iv according to McAfee classification.	HO was 44.6%(95% confidence interval (CI) 37.2-45.6%)- 12 months after ACDR 58.2%(95%CI, 29.7-86.8%)-24 months afterACDR Advanced HO- 11.1% (95%CI- 5.5 -16.7%) after 12 months 16.7%(95% CI, 4.6-28.9%) -after 24 months	Higher prevalence of HO was observed following ACDR but HO doesn't effect clinical improvement.
Brenke C etal (32)	22 patients were treated with ACDR	Severe HO grade iii or iv was present in 17.4 %	But the clinical outcome remains normal.NDI & VAS score improved significantly.2.4+/-2

			.5(arm) Mean VAS -3.8+/-2.7 (neck) Mean NDI- 30 +/-22
Lee SE etal(33)	28 patients underwent ACDR	18 patients(64.3%)of 28 had HO Grade i- 6 patients Grade ii-8 patients Grade iii – 3 patients Grade iv-1 patient HO was proportional to the time of follow up.	Cervical ROM was preserved in grade i and ii but restricted in grade iii and grade iv HO Clinical improvement according to VAS, NDI was not significantly correlated with the occurrence of HO.
Lingde K etal(34)	Total 38 patients were included .	Pooled data showed that the prevalence of HO after ACDR within 1 to years , 2to 5 years , and 5 to 10 years of follow up was38.0% , 52.6% & 53.6%. Prevalence of severe Ho was 10.9%,22.2%,& 47.5%, respectively .	This meta - Analysis reported that follow up time was positively associated with prevalence of severeHO (p<0.01),and 1 month growth of mean follow- up went with 0.63% increase of severe HO .
(35)Jin YJ et al	81 patients after 95 cervical arthroplasties using Bryan (35 segments, PCM(30 segments), Prestige (30 segments)	According to type of device incidence of HO was Bryan 49%- PCM 80%- Prestige 60%-	Type i HO developed mostly in posterior disc space. Type ii. HO developed in anterior disc space Type iii HO developed only in anterior disc space Cervical lordotic angle at 1 month after surgery had a significant

			connection with occurrence of type ii HO.
Xiaoyu Y .et al (36)	Not Available	At 2- year follow- up , occurrence of HO - 68 % in activC disc group (severe HO 55%) HO - 85% (p=0.12) Bryan disc group (severe HO 44 % ; p=0.43)	HO is independent on the architecture of cervical disc prosthesis . The global ROM - significantly higher in Bryan group (56+_10.8 degree) and (49.5+_14.0,P=0.04 4) ,however this difference was not clinically important ,because the clinical condition of both groups comparable . And presence of HO did not affect clinical outcome.

Discussion : Although spine surgeons have defined HO as clinically relevant and nonrelevant , this terminology seems to be based on ROM and don't impact clinical outcomes .It should be more accurately defined as motion restricting and non motion restricting HO .There is no literature analysis available ,which could defined the potential surgical intervention and prosthesis - specific reason behind HO after Artificial Cervical disc replacement surgery .Additionally , other possible predictors such as adjacent segment degeneration , Sagittarius alignment and operative levels need to be investigated further .(36).

Heterotopic ossification can be further classified in to genetic and acquired subtypes .Acquired HO is common complication of major connective tissue injury ,traumatic central nervous system injury , and surgical interventions ,where it can cause severe pain and

post operative disability . A highly destructive form of HO is seen in fibrodysplasia ossificans progressiva(FOP), in which progressive bone formation throughout life leads to painful and disabling immobility .Additionally , key role of stem / progenitor cell in HO is already established but little number of facts known about the mechanisms that control these progenitor cells for bone and cartilage formation. Moreover, we are not able to identify the offending cell type (s) so far .(37))

Zhou et al concluded that incidence of postoperative HO is relatively higher among the patients with more than 10 years follow-up ,and amount of degeneration in the target level before surgery also correlated with HO incidence .(38)

About 10 % of HO is symptomatic resulting in limitations in range of motion (ROM). Once Acquired HO develops ,surgical removal is the only effective treatment , usually followed by NSAIDs (non steroidal anti- inflammatory agents) or local radiation to avoid recurrence. (39).

However , radiation has been associated with malignancies , surgical removal is costly enough and efficiency of NSAIDs is variable in different cases .(40,41)

HJ Cho et al selected 87 patients who underwent anterior cervical surgery (TDR or ACIF anterior cervical Interbody fusion) and followed up more than 24 months .HO was observed in both TDR ACIF groups.HO was frequently occurred in TDR group .HO does not depend on prosthesis type . In ACIF group , only cage alone subgroup showed HO , with relation to fusion status . (42)

Additionally ,HO occurs following mechanical trauma ,burns ,orthopedic surgeries and in patients with hyperactivating mutations of the type 1 bone morphogenetic protein receptor ACVR1(Activin type 1 receptor).Here they demonstrate that hypoxia inducible factor -1alpha (Hif1 alpha), a key mediator of cellular adaptation to hypoxia , is highly expressed

and active in three separate mouse models : hybrid model of genetic and trauma induced HO , Trauma induced HO , genetic induced HO. Expression of Hif1 alpha coincides with master transcription factor of cartilage Sox9.[(sex determining region Y) - box9]. Application of pharmacologic agents, such as PX - 478 or rapamycin significantly inhibited extraskeletal bone formation through Hif1alpha inhibition .These findings indicated that Hif1 alpha represents a promising target to prevent and treat pathologic extraskeletal bone formation .(43)

Another study compared the long term clinical effect of ACDR & ACDF (Anterior cervical discectomy and fusion) in the treatment of degenerative cervical spondylosis in 60 patients , who received ACDR (n=27) and ACDF (n=33) .The incidence of HO in ACDR group was 92.6 % and high grade HO was 37.0 % . At minimum follow up of 10 years , ACDR achieves a satisfactory clinical effect compatible with ACDF .In terms of advantages , ACDR could maintain ROM of cervical segments and surgical segment both , which reduces ASD occurrence by preserving motion .(44)

Cao et al study showed average follow up time of 70 patients was (62.7 \pm 4.8) years (range , 52-74 months) .they found a significant positive correlation between preoperative uncovertebral joints degeneration and HO after ACDR ($r=0.585, p<0.01$) .There was a significant positive correlation between preoperative intervertebral space degeneration and HO ($r=0.557, p<0.01$) .There was significant positive correlation between preoperative intervertebral space degeneration and preoperative uncovertebral joints degeneration ($r=0.727, p<0.01$) . In a nutshell, There is a significant correlation between preoperative uncovertebral joints degeneration and HO after ACDR .(45)

In our study ,table 1. Shows that HO is a continuous process .but it does not restrict the motion of ACDR in any study , however it's an unavoidable complication of ACDR .

Several limitations should be considered ,whenever findings of this study interpreted .First , our study can not clarify the significant relationship between occurrence of HO and male sex , old age , multi segmental operations ,etc.Second, only few studies provide enough information about characteristics of patients with HO.Thirdly , selected studies are heterogenous in nature , and this heterogeneity can't be defined clearly .Last but not the least , language itself a limitation factor , because of which , some useful studies may be missed .

In order to get a better understanding about HO occurrence ,This information is useful for surgeons and patients both .On the other hand ,all selected studies in this review are lacking uniformity in nature .Hence the result of this review study should be considered prudently .

Abbreviations :

FOP: fibrodysplasia ossificans progressiva

TCM : Traditional Chinese Medicine .

Hif - alpha :hypoxia inducible factor -1alpha

HO: Heterotopic ossification

ACDR: Artificial cervical disc replacement

ACDF : Anterior cervical discectomy and fusion

ACVR1:Activin type 1 receptor .

ACIF :anterior cervical Interbody fusion

NSAIDs :Non Steroidal Anti- Inflammatory Agents

ASD:Adjacent Segment degeneration .

ROM : Range of motion .

NDI :Neck Disability Index

VAS:Visual Analog Scale

CI : Confidence Interval

TDR : Total Disc Replacement

IVD: Inter vertebral Disc

NP: Nucleus pulposus

References:

- (1)JA Buckwalter , " Spine update : aging and degeneration of the human intervertebral disc , " Spine , 20 (11):1307-1314;1995
- (2)M Haefeli , F Kalberer,D Saegesser etal . The course of macroscopic degeneration in the human lumbar intervertebral disc .Spine 31(14):1522-1531;2006
- (3)Smith GW, Robinson RA. The treatment of certain cervical spine disorders by anterior removal of the intervertebral disc and Interbody fusion .J Bone Joint Surg Am 1958;40 -A:607-24
- (4)Bartels R , Goffin J. Albert D. & Joseph CM.description of anterior cervical discectomy with fusion in 1955. J Neurosurgery Spine 2018 ; 28:395-400.
- (5)Cloward RB .The anterior approach for removal of ruptured cervical disks. J Neurosurg 1958;15:602-17
- (6)Goffin J , Geusens E, Vantomme N et al.Long term follow up after Interbody fusion of the cervical spine . J Spinal Disorder Tech 2004;17:79-85

- (7) Janssen ME , Zigler JE , Spivak JM et al. ProDisc - C total disc replacement versus anterior cervical discectomy and fusion for single - level symptomatic cervical disc disease : seven- year follow- up of the prospective Randomized U.S. Food and Drug Administration Investigational Device Exemption study . J Bone Joint Surg Am 2015 ; 97:1738-47.
- (8) Park JH, Roh KH, Cho JY et al. Comparative analysis of cervical arthroplasty using mobi - c (r) and anterior cervical discectomy and fusion using the solis (r) - cage . J Korean Neurosurg Soc 2008;44:217-21.
- (9) Hou Y , Nie L, Pan X et al. Effectiveness and safety of Mobi- C for treatment of single - level cervical disc spondylosis: a randomised control trial with a minimum of five years of follow -up . Bone Joint J 2016;98-B: 829-33
- (10) Zhang H- X , Shao Y- D , Chen Y , et al . A prospective , randomized , controlled multicenter study comparing cervical disc replacement with anterior cervical decompression and fusion . Int Orthop 2014;38:2533-41.
- (11) Coric D , Kim PK , Clemente JD et al. Prospective randomised study of cervical arthroplasty and anterior cervical discectomy and fusion with long- term follow up : results in 74 patients from a single site . J Neurosurg Spine 2013;18:36-42
- (12) Parkinson JF , Sekhon LH . Cervical arthroplasty complicated by delayed spontaneous fusion . Case report . J Neurosurg Spine 2005 ; 2:377-80.
- (13) Bartels RH, Donk R . Fusion around cervical disc prosthesis case report . Neurosurgery 2005 ; 57:E149; discussion E .
- (14) Dwivedi A, Dwivedi SS , Tariq MR , et al Conservative treatment of traumatic lower back pain : Case report and Literature Review . J Clin Exp Orthop .2019;5(2):68.
- (15) SC Slade , JL Keating . Unloaded movement facilitation exercise compared to no exercise or alternative therapy on outcomes for people with non Specific lower back pain : a systematic review . Journal of Manipulative and Physiological Therapeutics .2007;30(4):301-311
- (16) X Yang & X Li . Nucleus pulposus tissue engineering : a brief review . European Spine Journal . 2009;18(11):1564-1572
- (17) Dwivedi A, Dwivedi SS , Su Zhenhong, et al . Open reduction and internal fixation of posterior pilon variant fractures with buttress plate through posterolateral approach . IJCMR 2019;5:1-5

- (18) Dwivedi A , Dwivedi SS, Tariq MR et al .Stem cell regenerative medicine (SCRM)- A new hope in orthopedics - Review article .J Stem Cell Biol Transplant 2019;3:1-4
- (19) Dwivedi A ,Jian WX, Dwivedi SS, et al.Pilon fracture : An unsolved riddle : An updated review . IJCMR 2017 ;4:718-725
- (20)Dwivedi A , Jian WX, Dwivedi SS . Artificial cervical disc replacement : A double edged sword - A clinical review. IJCMR 2017;4:1163-1168.
- (21)Dwivedi A,SS Dwivedi,MR Tariq et al.General idea About the reach of Stem Cell Regenerative Medicine : Evidence Based Review ,J Res Med Dent Sci , 20202,8(4):57-64
- (22)Dwivedi A ,SS Dwivedi , MR Tariq et al.Traumatic Brain Injury and Stem Cell Therapy .J Res Med Dent Sci , 2020 .8(3):94-96
- (23)SK Jha , Dwivedi A , Kumar A ,etal .Stem cell therapy against COVID-19 .J Res Med Dent Sci , 2021,9 (11):14-20
- (24) Barna M, Stulík J, Kryl J, Vyskočil T, Nesnídal P ProDisc-C Total Disc Replacement. A Four-Year Prospective Monocentric Study]. Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca [2012, 79(6):512-519] Type: Journal Article, English Abstract
- (25)Yi S, Kim KN, Yang MS, Yang JW, Kim H, Ha Y, Yoon do H, Shin HCDifference in occurrence of heterotopic ossification according to prosthesis type in the cervical artificial disc replacement. Spine [2010, 35(16):1556-1561] Type: Journal Article, Research Support, Non-U.S. Gov't, Comparative Study DOI: 10.1097/BRS.0b013e3 181c6526b
- (26) Guérin P, Obeid I, Bourghli A, Meyrat R, Luc S, Gille O, Vital JM Heterotopic ossification after cervical disc replacement: clinical significance and radiographic analysis. A prospective study. Acta Orthopaedica Belgica [2012, 78(1):80-86] Type: Journal Article
- (27) Wu JC, Huang WC, Tu TH, Tsai HW, Ko CC, Wu CL, Cheng H Differences between soft-disc herniation and spondylosis in cervical arthroplasty: CT-documented heterotopic ossification with minimum 2 years of follow-up. Journal of Neurosurgery. Spine [2012, 16(2):163-171] Type: Journal Article DOI: 10.3171/2011.10.SPINE11497
- (28)Tu TH, Wu JC, Huang WC, Guo WY, Wu CL, Shih YH, Cheng H Heterotopic ossification after cervical total disc replacement: determination by CT and effects on clinical outcomes. (Journal of Neurosurgery. Spine [2011, 14(4):457-465] Type: Journal Article, Research Support, Non-U.S. Gov't DOI: 10.3171/2010.11.SPINE10444
- (29)Wu JC, Huang WC, Tsai TY, Fay LY, Ko CC, Tu TH, Wu CL, Cheng H , Spine [2012, 37(20):E1251-9] Multilevel arthroplasty for cervical spondylosis: more heterotopic ossification at 3 years of follow-up. Type: Journal Article DOI: 10.1097/BRS.0b013 e318265a126
- (30)Mehren C, Suchomel P, Grochulla F, Barsa P, Sourkova P, Hradil J, Korge A, Mayer HM Heterotopic ossification in total cervical artificial disc replacement. (PMID:17108833) Spine [2006, 31(24):2802-2806] Type: Clinical Trial, Journal Article, Multicenter Study DOI: 10.1097/01.brs.0000245852.70594.d5

(31)Chen J, Wang X, Bai W, Shen X, Yuan W Prevalence of heterotopic ossification after cervical total disc arthroplasty: a meta-analysis. European Spine Journal: Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society [2012, 21(4):674-680] Type: Journal Article, Meta-Analysis, Review (PMID:22134486) OI: 10.1007/s00586-011- 2094-x

(32)Brenke C, Scharf J, Schmieder K, Barth M High prevalence of heterotopic ossification after cervical disc arthroplasty: outcome and intraoperative findings following explantation of 22 cervical disc prostheses. Journal of Neurosurgery. Spine [2012, 17(2):141-146] Type: Journal Article, Review, Case Reports DOI: 10.3171/2012.4.SPINE12223

(33)Lee SE, Chung CK, Jahng TA Early development and progression of heterotopic ossification in cervical total disc replacement. (PMID:21999390) Type: Journal Article DOI: 10.3171/2011.8.SPINE11303 Journal of Neurosurgery. Spine [2012, 16(1):31-36]

(34)Lingde k, Qinghua M, Fei M et al .The prevalence of Heterotopic ossification among patients after cervical artificial disc replacement . Medicine .2017;96(24);e7163

(35)Jin YJ, Park SB, Kim MJ, Kim KJ, Kim HJ An analysis of heterotopic ossification in cervical disc arthroplasty: a novel morphologic classification of an ossified mass The Spine Journal: Official Journal of the North American Spine Society [2013] Type: Journal Article.

(36) Xiaoyu Y. Roland D , Ronald HMA Bartels .et al. Comparing Heterotopic Ossification in two Cervical Disc Prosthesis .Spine 2020;45 (19): 1329-1334

(37)John BLS , David J G .Stem Cells and Heterotopic Ossification :Lessons from Animal Models .Bone .2018; 109 : 178-186

(38)Zhou FF , Li SY , Zhao YB . Quantitative analysis of the degeneration of cervical spine and correlation to the Heterotopic ossification after artificial cervical disc replacement .Zhonghua Yi Xue Za Zhi .2021; 101(13):945-949

(39) N. Cullen and J Perera .Heterotopic ossification: pharmacologic options .Journal of Head Trauma Rehabilitation . 24(1):69-71;2009

- (40)UM Carl & KA Hartmann .Heterotopic calcification as a late radiation effect : report of 15 cases .British Journal of radiology 75 (893): 460-463;2002.
- (41)VD Pellegrini Jr. And CM Evarts . Radiation prophylaxis of Heterotopic bone formation following total hip arthroplasty : current status .Seminars in Arthroplasty. 3.(3):156-166;1992.
- (42)Cho HJ, Shin MH , Huh JW et al .Heterotopic ossification following cervical total disc replacement : iatrogenic or constitutional ? Korean J Spine 2012 ;9(3):209-14
- (43)Agarwal S , Loder S , Brownley C et al .Inhibition of Hif1alpha prevents both trauma - induced and genetic Heterotopic ossification . Proc Natl Acad Sci U S A. 2016 : 19;113(3):E338-47.
- (44)Wang F, Shen Y , Du W. Long term outcomes of Bryan artificial cervical disc replacement for degenerative cervical spondylosis .Zhonghua Yi Xue Za Zhi .2020;8 ;100(45):3602-3608
- (45)Cao S , Pan SF , Sun Y et al .The correlation between the severity of uncovertebral joints degeneration and Heterotopic ossification after single - level artificial cervical disc replacement .Zhonghua Yi Xue Za Zhi .2020;8;100(45):3578-3583